SPECIAL ARTICLE

Are genes destiny? Have adenine, cytosine, guanine and thymine replaced Lachesis, Clotho and Atropos as the weavers of our fate?

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It is as futile to ask how much of the phenotype of an organism is due to nature and how much to its nurture as it is to determine how much of the area of a rectangle is due to its length and how much to its height. Phenotype and area are joint products. The spectacular success of genomics, unfortunately, threatens to re-awaken belief in genes as the principal determinants of human behavior. This paper develops the thesis that gene expression is modified by environmental inputs and that the impact of the environment on a given organism is modified by its genome. Genes set the boundaries of the possible; environments parse out the actual.

Key words: Genomics, ontogenetic niche, polyphenism, collective efficacy, heritability, phenylketonuria, thalassemia, gene regulation, Williams syndrome

When I completed my psychiatric training in the United States, more than a half century ago, genetics was anathema. Psychoanalysis was viewed as the cutting edge of psychiatry and excited the best and the brightest of young residents.

Fifty years later, psychiatry in the United States has been turned upside down. The discovery of psychotropic drugs has transmuted psychiatrists into psychopharmacologists. Despite extensive evidence that manualized psychotherapies (cognitive behavior therapy and interpersonal psychotherapy) are as effective as tricyclics and selective serotonin reuptake inhibitors for mild and moderate depression, interest in psychological treatments continues to wane.

Prodigious advances in neuroscience and in brain imaging have yielded a dynamic model of a brain that is shaped by experience and continues to change over the life course. To cap the revolution, the mapping of the human genome promises to make it possible to identify genes that influence risk and resistance to psychiatric disorders. Discoveries in neuroscience and genomics continue the reshaping of psychiatry into a disproportionately biological specialty where it had once been a disproportionately psychosocial specialty.

Despite the one-sidedness, the gains in our science base constitute a very considerable advance over the days when I was trained. What is unacceptable in the "new" psychiatry is a naïve genetic determinism that fails to take social context into account, just as the "old" psychiatry ignored biology. Just as I was troubled by psychoanalytic exclusivism then (brainless psychiatry), I am troubled by the dominance of a fixation on biology (mindless psychiatry) that ignores social context (1). The aim of this paper is to reiterate the central principle of evolutionary genetics: just as the unique response of the organism to its environment depends on its genome, the expression of that genome is conditioned by that environment.

GALTON'S "CONVENIENT JINGLE"

In his study of "English Men of Science", Francis Galton (2) sought to discriminate the influence of heredity from that of environment. Viewing the relationship between the two as dichotomous and competitive, he wrote: "The phrase 'nature and nurture' is a convenient jingle of words ... it separates under two distinct heads the innumerable elements of which personality is composed. Nature is all that a man brings with himself into the world; nurture is every influence from without that affects him after his birth…When nature and nurture compete for supremacy on equal terms… the former proves to be the stronger … [although] neither is self-sufficient."

Will detailed knowledge of the genome foretell the future of our children? In Greek mythology, three figures wove the tapestry of human fate: Lachesis, the measurer, allotted to each his portion; Clotho, the spinner, spun out the threads of life; and Atropos, the lady of the shears, severed the thread at the appointed time. Similar myths abound in other cultures. In the Icelandic sagas, man's fate is determined by the witches, Urdur, Verdandi and Skuld. How far do these ancient myths foretell the truth? Are adenine, cytosine, guanine and thymine the weavers of our fate?

To put the question in these terms is to enthrone Galton's jingle. To ask how much of the phenotype is due to nature and how much to nurture is as profitless as to ask how much of the area of a rectangle is due to its length and how much to its width. Every phenotypic trait reflects the outcome of gene expression in particular environments.

Of course, there are limiting cases at either extreme; that is, there are lethal genes (mutations incompatible with fetal viability) and environments lethal to every genome. When tons of carbon dioxide erupted from Lake Nyos in Cameroon on August 21, 1986, the cloud suffocated everything in its path as it rolled down the hill. By next morning, 1700 people and countless animals were dead (3). There were no gene-based exceptions. In most clinical circumstances, however, the gene effects we encounter have been modified by the environments the organism has experienced and the environmental effects

we see are dependent on the genomes of the organisms they have acted upon.

THE ONTOGENETIC NICHE

Nature and nurture stand in reciprocity, not opposition. Offspring inherit, along with their parents' genes, their parents, their peers, and the places they inhabit. West and King (4) have coined the term "ontogenetic niche" to emphasize that organisms develop within an ecological and social setting that, like their genes, they share with their parents. It helps us recognize that neighborhood and neighbors matter along with parents and siblings. The ontogenetic niche is a legacy that guides development, a crucial link between parents and offspring, an envelope of life chances. Replacing the rhetorical contrast "nature versus nurture" with "nature, niche, and nurture" emphasizes the conjunctions rather than the oppositions that shape the developmental trajectory.

The impact of neighbors and neighborhood as niche is clearly evident in the findings of the Project on Human Development in Chicago Neighborhoods (5). Tony Earls and his colleagues (6) knew that certain characteristics of neighborhood structure – the concentration of poverty, the extent of ghettoization, residential instability – account for a significant amount of the variance in adolescent antisocial behavior (7). However, what they were able to show by the use of sophisticated statistical methods is that, after adjusting for prior levels of neighborhood crime, informal social control emerged as a significant deterrent to adolescent delinquency (8). "Informal social control" refers to the likelihood that adults in the community will monitor spontaneous children's play groups, intervene to prevent truancy and street corner hanging out by teenagers, and confront persons misusing or disturbing public space. Further, informal social control reflects the ability of cohesive communities to demand needed resources from city authorities for police patrols, fire stations, garbage collection and housing code enforcement. The importance of this power is apparent from the correlation between abandoned housing, burned out buildings, graffiti and litter in an area and more serious crime.

"Collective efficacy" is the term proposed for the social cohesion among neighbors willing to act on behalf of the common good. Unstable and poverty-stricken neighborhoods with high concentrations of recent immigrants display low collective efficacy. In turn, low efficacy itself mediates a substantial part of the association between disadvantage and violence. The ecology of neighbors and neighborhood interact with family characteristics to determine behavioral outcomes (5).

CALCULATING HERITABILITY

Before the specific genes have been identified, geneticists commonly employ a measure termed "heritability" to partial out the genetic contribution to a trait of interest. This measure disregards variance arising from genotype-environment interactions, from assortative mating, and from interactions between genes (that is, different loci do not always act in additive fashion). Beyond matters of methodology, research on humans is constricted by the limited range of environments to which given populations have been exposed (in contrast to agricultural research, where soil, temperature, sunlight, irrigation, fertilizer, as well as plant genotype, can be systematically modified). Estimates of "heritability" reflect no more than the findings on a specified population sampled in a given geographic range during a particular historical era (9). Rather than being a statistic applicable to all populations at all times, heritability estimates are context-bound and may be higher or lower (or perhaps even unmeasurable) in other populations, in other places, at other times.

When phenocopies abound, heritability will be low or unmeasurable in such circumstances. Gene effects may become evident only after environmental variance has diminished. When changes in the environment diminish the extrinsic causes of a disease without eliminating that disease altogether, the remaining cases will show a larger heritability (10). Secular changes in the epidemiology of rickets offer a telling example.

Rickets was endemic in the United States in the 1920s. The discovery of vitamin D and the provision of D-enriched milk resulted in a dramatic decrease in the prevalence of rickets. Thus, Albright and his colleagues (11) first reported D-resistant rickets in 1937, the genetic signals previously having been unrecognizable amidst the environmental noise resulting from phenocopies. As improved living conditions in industrialized countries removed exogenous causes, the heritability of rickets increased – from undetectable levels toward one! Yet, exogenous rickets persists, albeit at a low rate, among such populations as Muslim women who continue to cover almost all their skin surfaces with clothing after moving to countries in the Northern hemisphere with less ambient sunlight; and homebound elderly patients in Boston and Edmonton during winter months when atmospheric attenuation of ultraviolet radiation in the 290-315 nm band limits vitamin D3 synthesis in the skin (12,13).

Although the "heritability" of height approaches 0.9, adult height in industrialized countries has increased by several inches during the last two centuries without significant perturbations in the distribution of the genes. Better nutrition and better health have allowed fuller expression of the growth potential already inherent in the genome. In contrast, malnourished children are stunted in growth; computed "heritability" in impoverished families is much lower.

If malnutrition influences the apparent "heritability" of height, what impact does socioeconomic deprivation have on the "heritability" of intelligence? The complexity of the relationship has been clarified in a recent study by

Eric Turkheimer and his colleagues (14). They analyzed intelligence test scores on a sample of 320 7-year old twin pairs, one third monozygotic. Their sample was unusual in that a substantial number of the children were raised in families near or below the poverty level. Few twin studies have included children from impoverished backgrounds. What were the new findings? In the author's words: "In impoverished families, 60% of the variance in IQ is accounted for by the shared environment and the contribution of genes is close to zero, whereas in affluent families, the result is almost exactly the reverse."

The calculated heritability of IQ for the children raised in middle class families was substantial (0.72), whereas heritability was barely detectable (0.1) among those in economically marginal families. The proportion of IQ variance attributable to genes, versus that attributable to environment, varies in a nonlinear fashion with socioeconomic status. The environment plays such a substantial role in the cognitive development of children growing up under deprived conditions that it obscures the genetic contribution to inter-individual variability. At or near threshold, small variations in biological and psychological input have a far more powerful effect than they do when inputs are nearly optimal. Just as inadequate food intake depresses statural height and lowers its measured heritability, affective and cognitive (as well as protein-calorie) malnutrition has similar effects on the development of intelligence. Whatever the environment, children will differ in intelligence because of genetic variance. That remains the case under growth-depressing as well as growth-promoting conditions. Because class differences reflect rearing conditions, the cognitive stunting associated with severe poverty is preventable!

POLYPHENISM

Genomic identity does *not* assure phenotypic identity. Very different phenotypes can arise from *identical* genomes, a phenomenon known as *polyphenism*; that is, the occurrence of several distinct phenotypes in a given species. Each phenotype develops facultatively depending upon cues from the internal and external environment. With changes in diet and season, dimorphic oak caterpillars express phenotypes so distinct that the two forms were originally classified as separate species. The difference between continuous phenotypic variation and discrete polyphenism is a complex underlying regulatory mechanism that controls a fork between divergent pathways. "The expression of a polyphenism begins when [extrinsic] signals are transduced into a *developmental switch* governed by the interplay of hormone secretion, hormone titre, sensitivity threshold to the hormone, timing of the hormone-sensitive period, and specific cellular responses to hormones" (15).

Female honeybee larvae differentiate into queens or workers with profound morphological differences despite identical genomes. Larvae that will become queens are reared in large vertically oriented brood cells. Queens are fed "royal jelly" by nurse bees, but there is no unique "royal" ingredient (16). What seems to matter are the large differences in the frequency, the amount, and the composition of feedings for queens. Genetically governed programs add their own effects downstream.

The developmental switch depends not on genomic differences between queens and workers, but on the differential expression of entire suites of genes. Distinct developmental differences in titres of insect terpenoid juvenile hormone and ecdysone become manifest as the growth rate of queens continues to outpace that of workers (17, 18). The ultimate phenotypic outcomes are morphologically, reproductively, and behaviorally distinct castes. Interplay between genome and socially organized behavior is exquisitely adapted to the local environment. Plentiful nutrition (or too little of it) induces polyphenisms in bees and oak caterpillars, as do day length and humidity in aphids and butterflies, and population density and predator presence in other arthropods.

POLYPHENISM AND HUMAN DEVELOPMENT

What does polyphenism in bees and butterflies have to do with human development? Charles Scriver (19) suggests that the term applies by analogy to clinical outcomes in which phenotypes differ strikingly despite identity in genes which ordinarily are decisive. Consider two five-year-old patients with phenylketonuria, each with the null mutant gene for phenylalanine hydroxylase (PAH). The patient whose genetic defect has not been recognized will exhibit severe mental deficiency, psychotic behavior, and seizures. The patient who has been identified by metabolic screening in the newborn nursery and has been maintained on a low phenylalanine diet will be within the normal range. Both are homozygous for the autosomal recessive gene; yet, their phenotypes are extraordinarily different. In the clinical case, high blood phenylalanine levels derailed brain development. In the normal patient, dietary control has prevented the metabolic consequences of enzyme deficiency. Comparable "polyphenisms" can be seen when congenital hypothyroidism, galactosemia, maple syrup urine disease, or homocystinuria are detected by neonatal screening programs and are managed appropriately (20). Despite genotypic identity, phenotypic outcome in untreated and treated cases is as night to day.

Even in Mendelian disorders like phenylketonuria, the relationship between genotype and phenotype is complex. More than 400 different mutations have been identified in the PAH gene (deletions, insertions, splicing defects, missense and nonsense mutations). Most phenylketonurics are compound heterozygotes, having inherited different mutations from each parent. Yet, without intervention, the phenotype of the compound heterozygote is grossly abnormal. The principal determinant of the phenotype in what

is unequivocally a genetic disorder is the social environment: namely, access to metabolic control through diet, the age at which it is achieved, and the degree of control attained.

GENE-GENE INTERACTIONS IN MENDELIAN DISORDERS

Complexity in phenylketonuria is as nothing compared to the remarkable phenotypic diversity in the beta thalassemias. These monogenic blood disorders arise from defective beta-globin synthesis; as a result, the excess of alpha chain aggregates in red cell precursors and leads to abnormal cell maturation and premature cell destruction. At one end of the clinical spectrum, profound anemia results in foetal or neonatal death; at the other, "silent" beta thalassemia mutants may be an incidental finding in family studies. Phenotypic diversity in the beta thalassemias reflects "layer upon layer of complexity" (21).

To begin with, there are *more than 200 primary mutations* in beta-globin genes, each with different quantitative effects: most are recessive; a few are dominant.

In the second place, there are *modifying genetic loci*: those for alpha-globin and for fetal hemoglobin persistence. Comorbid alpha thalassemia can lessen the severity of beta thalassemia by diminishing the alpha chain excess. Thalassemic patients with persistent fetal hemoglobin have milder disease because the gamma chains of hemoglobin F bind the alpha excess.

The genes that control bilirubin, iron, and bone metabolism are *tertiary modifiers*. The heme products resulting from red cell destruction induce jaundice and gallstone formation; polymorphisms in the promoter gene controlling *hepatic glucuronidation* of bilirubin can ratchet disease severity up or down. Iron loading compromises cardiac, hepatic, and pancreatic function. *HFE polymorphisms* influencing intestinal iron absorption modify the severity of heart failure, cirrhosis, and diabetes. The progressive osteoporosis seen in adult thalassemics occurs because iron is toxic to the hypothalamic-pituitary axis. The iron toxicity can be slowed down or hastened by alleles for the vitamin D receptors, estrogen receptors, and collagen.

Fourth, variations in mutant gene frequencies in different populations reflect the *evolutionary effects of coselection* because of heterozygote advantage against *P. falciparum* malaria.

Finally, features of the *social environment* (comorbid infection, malnutrition, and lack of access to medical care) worsen clinical outcomes. If such is the case in "simple" Mendelian disorders, an even higher degree of complexity will characterize multifactorial disorders.

PARENTING AND GENE REGULATION

How is social experience transmuted into development? There is a two-way traffic between genes and behavior. In rats, maternal licking, grooming, and nursing behavior (LGN) shapes endocrine and behavioral stress responses in offspring (22,23). Adult offspring of high LGN dams are less fearful and show diminished hypothalamic-pituitary-adrenal responses to stress. The female pups of high-LGN dams become high-LGN dams themselves, suggesting genes at work. However, when female pups born to low-LGN dams are cross-fostered to high-LGN dams, they too become high-LGN dams. Maternal behavior has been transmitted across generations by nongenomic means – if you will, by "culture". How does that happen? Maternal care regulates gene expression in brain regions controlling stress responses. Pups exposed to high-LGN display increased hippocampal glucocorticoid receptor mRNA expression, higher central benzodiazepine receptor levels in the amygdala, and lower corticotropin releasing factor mRNA in the paraventricular nucleus of the hypothalamus. Social experience alters gene expression for the long term.

A contrasting example is provided by studies of voles, rodents similar to mice (23). Vole species vary markedly in their social behavior. The prairie vole is social and monogamous; the montane vole is asocial and promiscuous. In the male prairie vole, mating stimulates secretion of the hormone arginine vasopressin (AVP). The release of AVP is associated with pair bonding and paternal care. Does the social behavior result from AVP release? Blockade of the vasopressin receptor V1a in the brain prevents both bonding and parenting responses to mating; intraventricular injection of AVP increases affiliative behavior. The pathway from mating behavior to bonding behavior is hormonal. In contrast, administration of AVP has no effect on the montane vole. The structure of the genes controlling the V1a receptor in the brain differs in the two species; the montane vole V1a gene lacks a 428 base-pair coding sequence found in the prairie vole gene. Gene structures determine and refract behavior patterns.

GENES AS MAJOR DETERMINANTS OF BEHAVIOR

Structures govern functions even as function molds structures. Genes matter greatly; in some syndromes, they are decisive. Gene-based abnormalities can result in "behavioral phenotypes". Williams syndrome (WS) is such an instance; it is characterized by an unique behavioral phenotype: severe visual-spatial defects in the presence of enhanced face processing and emotionality. Wechsler performance IQ is significantly lower than verbal IQ. Some WS children exhibit what has been termed "cocktail speech"; that is, fluent, articulate speech with many clichés, social phrases, and irrelevancies (24). The cause of WS is an interstitial gene deletion on chromosome 7; the size of the deletion varies, and so do the clinical manifestations.

Allan Reiss and his colleagues (25) used high resolution magnetic resonance imaging to look at differences in brain structure by comparing 43 patients with WS with 40 age-

and gender-matched controls. The brain volume of WS patients was 11% smaller than that of controls. Reductions in volume and gray matter density were even greater in the brain regions that play a role in visual-spatial processing (thalamus and occipital cortex). In contrast, WS patients had disproportionately *larger* volumes and *increased* gray matter density in structures known to play a major role in emotional and social behaviors (amygdala, cingulate cortex, superior temporal gyrus, fusiform gyrus, and insular cortex). The pathways from the gene deletions on chromosome 7 to the abnormalities in structure remain to be discovered. It is evident, however, that the abnormal structures go a long way toward accounting for the behavioral phenotype.

GENE/ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA

It has long been evident that the schizophrenias are familial. Risk among first degree relatives of persons with schizophrenia is an order of magnitude higher than it is in the general population. But what is the mode of transmission? Although hints abound, there is still no decisive evidence on the genes that confer risk. Even without precise identification of the genes, however, following the course of young children adopted away from mothers with schizophrenia offers a way to examine the gene/environment interactions. By far the best study of this problem by the adoption method was published in the spring of 2004.

Pekka Tienari and his colleagues (26) at the University of Oulu in Finland have reported a long-term follow-up study of Finnish adoptees, half of whom were born to mothers who were schizophrenic. The investigators derived their sample from a Finnish population register that listed all admissions to psychiatric hospitals as well as all adoptions that had taken place over a 20-year time interval. They identified 145 mothers with schizophrenia who had given birth to a child placed for adoption. The adoptee sample was matched demographically with adoptees whose mothers had no history of psychiatric hospitalization. They examined both sets of adoptees and their adopting families on carefully calibrated psychometric instruments when the adoptees had reached a median age of 23 and again when they were 35. The findings provide striking evidence for both hereditary and environmental influences.

Whereas only 8 of the 145 children born to normal mothers had become schizophrenic, 27 of those born to mothers with schizophrenia had. This highly significant difference is clear testimony to a major hereditary contribution. However, assessing the families who had reared the children yielded an equally interesting finding: namely, that 27 of the 32 adoptees who became schizophrenic had grown up in dysfunctional adoptive families.

These results suggest either that healthy child rearing diminishes the likelihood that the schizophrenic phenotype will become manifest despite genetic risk or that the expression of genetic risk requires environmental precipitants. Pekka Tienari and his colleagues could not exclude "reverse causality"; that is, the possibility that inherited biological peculiarities in the high-risk adoptees had "induced" dysfunction in their adoptive families. Weighing all of the evidence, they conclude that "neither high genetic risk nor dysfunctional family environment alone predicts schizophrenia". What is decisive is the interaction of risk and rearing.

DEPRESSION ARISING FROM STRESS IN VULNERABLE PERSONS

It has long been known that stressful life events increase risk for depression. It is equally clear that only a minority of those exposed to stress develop clinical syndromes. Why do some succumb and others not? One obvious source is allelic variation. In the case of depression, a promising candidate is a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR), because length variation in its alleles affects serotonin uptake at the synapse.

Caspi and colleagues (27) employed data from the Dunedin Longitudinal Study of Development, which had assessed more than 1000 children biennially from age 3 to 21. Among the factors recorded was exposure to stressful life events, including abuse as a child. When the study subjects were examined at 26, 17% met criteria for a major depressive episode.

For a genetic analysis, the study subjects were divided into three groups based on their 5-HTTLPR genotype: a) homozygous for the short allele, b) heterozygous, and c) homozygous for the long allele. Stressful life events had a much greater impact on the likelihood of depression among those carrying at least one short allele than they did among those homozygous for the long allele. As further evidence for the role of genetic diathesis, a documented history of abuse as a child predicted depression only in those with a short allele (27).

CONCLUSION

The clinical examples provided in this paper (the inheritance of intelligence, phenylketonuria, schizophrenia and depression) foretell the great advances in psychiatry that are promised by advances in genetic science. At the same time, these examples make clear that clinical phenotypes reflect environments as well as genotypes. Indeed, success in specifying genotypes will make it easier for clinicians to identify the relevant features of the familial and nonfamilial environment that influence the likelihood of health and disease (28).

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